Formula I

wherein, as valence ~~and stability~~ permits,

R_2, R_3, R_4, and R_5, represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_6, R_7, and R'_7, are absent or represent, independently, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$, or

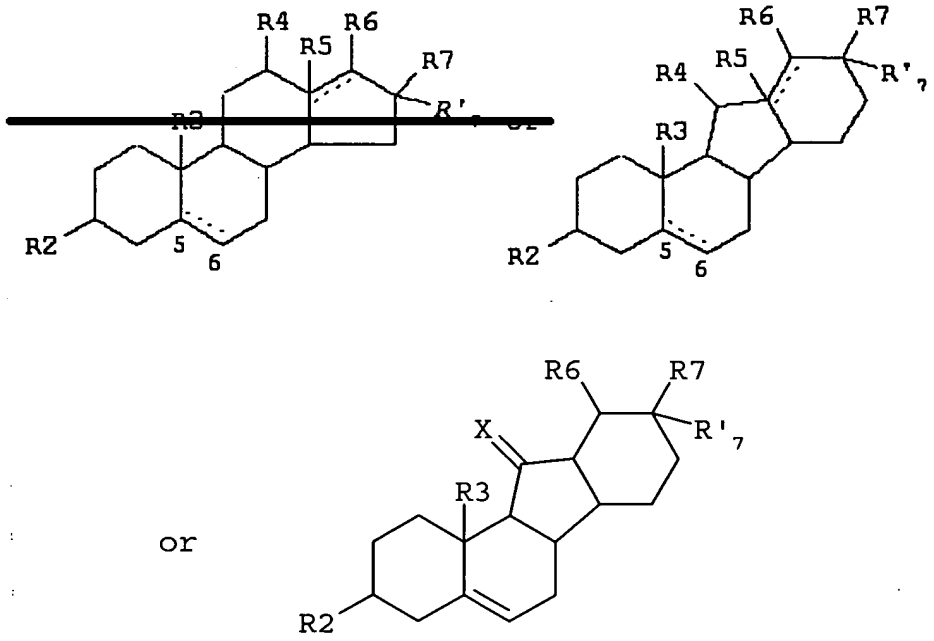
R_6 and R_7, or R_7 and R'_7, taken together form a ring or polycyclic ring~~, e.g., which is susbstituted or unsubstituted,~~;

with the proviso that at least one of R_6, R_7, or R'_7 is present and includes a primary or secondary amine;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

m is an integer in the range 0 to 8 inclusive.

5. (Amended) ~~The method of claim 1 or 2~~ A method for inhibiting unwanted hair growth or inhibiting spermatogenesis, comprising administering to a patient a composition comprising ~~wherein the hedgehog antagonist is~~ a purified steroidal alkaloid represented in the general formula (II), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula II

wherein ~~R_2, R_3, R_4, R_5, R_6, R_7, and R'_7 are as defined above, and~~

R_2, R_3, R_4, and R_5, represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_6, R_7, and R'_7, are absent or represent, independently, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$, or

R_6 and R_7, or R_7 and R'_7, taken together form a ring or polycyclic ring,

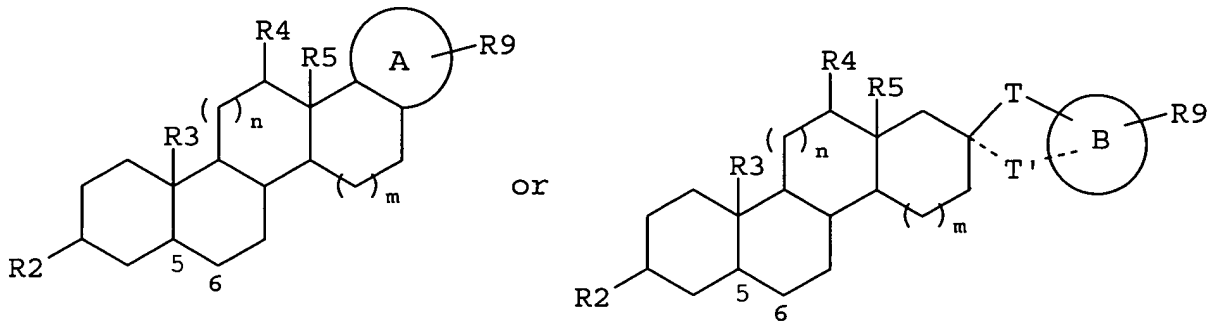
with the proviso that at least one of R_6, R_7, or R'_7 is present and includes a primary or secondary amine;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle;

m is an integer in the range 0 to 8 inclusive; and

X represents O or S~~, though preferably O~~.

6. (Amended) ~~The method of claim 1 or 2~~ A method for inhibiting unwanted hair growth or inhibiting spermatogenesis, comprising administering to a patient a composition comprising ~~wherein the hedgehog antagonist is~~ a purified alkaloid represented in the general formula (III), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula III

wherein

~~R_2, R_3, R_4, R_5 and R_8 are as defined above;~~

R_2, R_3, R_4, and R_5, represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle;

A and B represent monocyclic or polycyclic groups;

T represents an alkyl, an aminoalkyl, a carboxyl, an ester, an amide, ether or amine linkage of 1-10 bond lengths;

T' is absent, or represents an alkyl, an aminoalkyl, a carboxyl, an ester, an amide, ether or amine linkage of 1-3 bond lengths, wherein if T and T' are present together, than T and T' taken together with the ring ~~A or~~ B form a covaelently closed ring of 5-8 ring atoms;

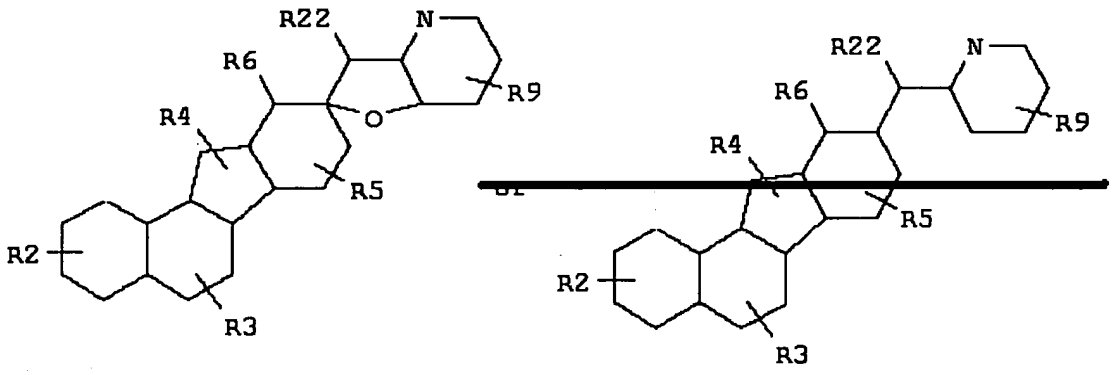
R_9 represent one or more substitutions to the ring A or B, which for each occurrence, independently represent halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl,

=O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or -$(CH_2)_m$-R_8; and

n and m are, independently, zero, 1 or 2;

with the proviso that A and R_9, or T, T' B and R_9, taken together include at least one primary or secondary amine.

7. (Amended) ~~The method of claim 1 or 2~~ A method for inhibiting unwanted hair growth or inhibiting spermatogenesis, comprising administering to a patient a composition comprising ~~wherein the hedgehog antagonist is~~ a purified steroidal alkaloid represented in the general formula (IV), or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula IV

wherein

~~R_2, R_3, R_4, R_5, R_6 and R_9 are as defined above;~~

R_2, R_3, R_4, and R_5, represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or -$(CH_2)_m$-R_8;

R_6 is absent or represents halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls,

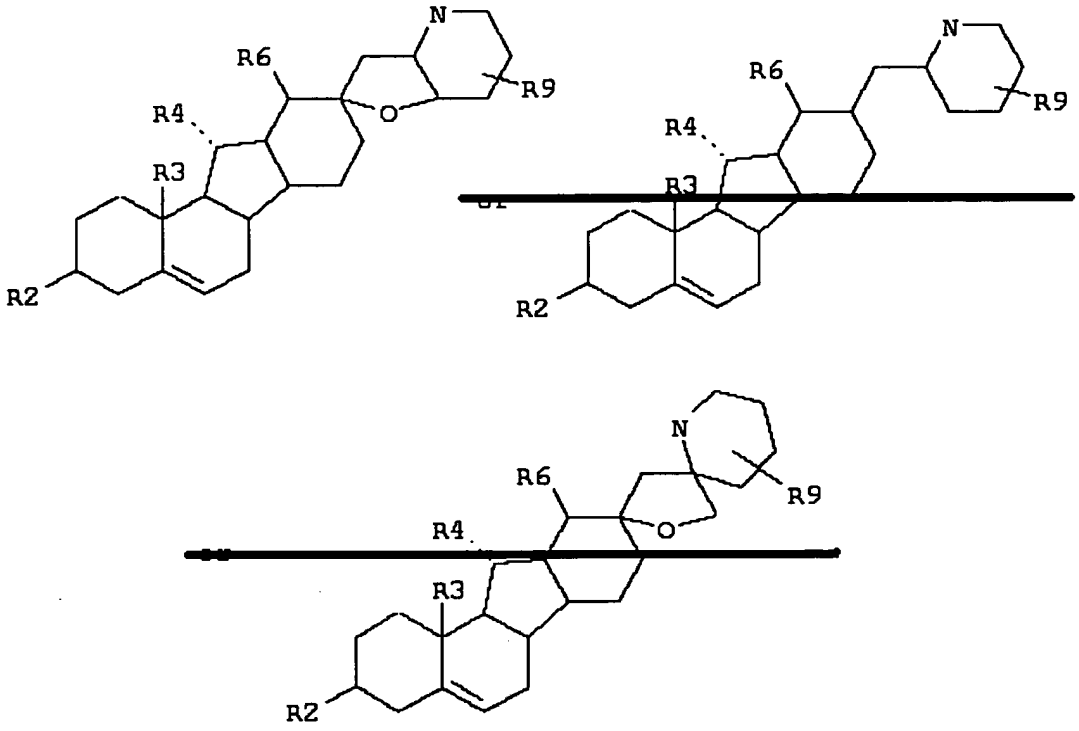
phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle;

R_9 represents one or more substitutions to the ring A or B, which for each occurrence, independently represent halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$; and

R_{22} is absent or represents an alkyl, an alkoxyl or -OH.

8. (Amended) ~~The method of claim 1 or 2~~A method for inhibiting unwanted hair growth or inhibiting spermatogenesis, comprising administering to a patient a composition comprising ~~wherein the hedgehog antagonist is~~ a purified steroidal alkaloid represented in the general formula (V) or unsaturated forms thereof and/or seco-, nor- or homo-derivatives thereof:



Formula V

wherein ~~R_2, R_3, R_4, R_6 and R_9 are as defined above;~~

R_2, R_3, and R_4, represent one or more substitutions to the ring to which each is attached, for each occurrence, independently represent hydrogen, halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_6 is absent or represents halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$;

R_8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle, or a polycycle; and

R_9 represents one or more substitutions to the ring A or B, which for each occurrence, independently represent halogens, alkyls, alkenyls, alkynyls, aryls, hydroxyl, =O, =S, alkoxyl, silyloxy, amino, nitro, thiol, amines, imines, amides, phosphoryls, phosphonates, phosphines, carbonyls, carboxyls, carboxamides, anhydrides, silyls, ethers, thioethers, alkylsulfonyls, arylsulfonyls, selenoethers, ketones, aldehydes, esters, or $-(CH_2)_m-R_8$.

12. (Amended) The method of any of claims ~~3-10~~ 3-8, wherein the steroidal alkaloid does not specifically bind a nuclear hormone receptor.

13. (Amended) The method of any of claims ~~3-10~~ 3-8, wherein the steroidal alkaloid does not specifically bind estrogen or testosterone receptors.

14. (Amended) The method of any of claims ~~3-10~~ 3-8, wherein the steroidal alkaloid has no estrogenic activity at therapeutic concentrations.

15. (Amended) The method of any of claims ~~1-10~~ 3-8, wherein the steroidal alkaloid ~~hedgehog antagonist~~ inhibits hedgehog-mediated signal transduction with an ED_{50} of 1 mM or less.

16. (Amended) The method of any of claims ~~1-10~~ 3-8, wherein the steroidal alkaloid ~~hedgehog antagonist~~ inhibits hedgehog-mediated signal transduction with an ED_{50} of 1 μM or less.

17. (Amended) The method of any of claims ~~1-10~~ 3-8, wherein the steroidal alkaloid ~~hedgehog antagonist~~ inhibits hedgehog-mediated signal transduction with an ED_{50} of 1 nM or less.

20. (Amended) The method of ~~claim 1 or 2~~any of claims 3-8, wherein the steroidal alkaloid~~hedgehog antagonist~~ is administered as part of a therapeutic or cosmetic application.

22. (Amended) The method of any of claims ~~1-7~~3-8, wherein the ~~hedgehog antagonist~~ steroidal alkaloid is applied as a topical formulation ~~to skin in order to inhibit aberrant proliferation of epithelial cells~~.

REMARKS

Following entry of the foregoing amendments, claims 3-8, 11-17, 20, 22, and 24-26 constitute the pending claims in the present application. The Examiner has withdrawn claims 2, 4, 9, 10, and 14-26 as being drawn to a non-elected invention. Applicants have canceled claims 1, 2, 9-10, 18, 19, 21, and 23 without prejudice and reserve the right to prosecute claims of similar or differing scope in subsequent applications. The amended claims 3-8 are directed to a method for inhibiting unwanted hair growth, comprising administering to a patient a composition comprising a *purified* alkaloid, as distinguished from methods utilizing alkaloids, such as jervine, as found in their natural sources. Amendments presented in this response are made solely to expedite prosecution of the claims in the present application. Applicants respectfully request reconsideration in view of the following remarks.

Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note that Applicants' arguments with respect to election with traverse of Group I and the species of cyclopamine in Paper No. 9 have not been found persuasive and the requirement has been made FINAL.

2. Applicants note that based on Applicants' election, claims 2, 4, 9, 10, and 24-26 stand withdrawn from further consideration as being drawn to a non-elected invention.

3. Claims 11-17 and 21-23 are objected to under 37 CFR 1.75(c) as being allegedly in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. Applicants have amended claims 3-8 to obviate this objection. Applicants submit that these amendments overcome the Examiner's objection. Reconsideration and withdrawal of this rejection is respectfully requested.

4-6. Claims 1, 3, 5-8 and 18-20 are provisionally rejected under the judicially created doctrine of double patenting over claims 3, 5-8, 11-17, 20, 30, 31, 43 and 44 of co-pending Application No. 09/090,622 and over claims 1 and 2 of U.S. Patent No. 6,288,048. Applicants have canceled claims 1, 18 and 19, solely to expedite prosecution of the remaining claims in the present application, rendering this rejection moot with respect to these claims. Applicants have amended claims 3 and 5-8 to obviate this rejection with respect to these claims and claims dependent thereon. Applicants submit that the amended claims are directed to subject matter not obvious in light of the subject matter claimed in the co-pending Application No. 09/090,622 and U.S. Patent No. 6,288,048. Reconsideration and withdrawal of this rejection is respectfully requested.

7-8. Claims 1 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds found in Figure 1, does not allegedly reasonably provide enablement for all hedgehog antagonists. Applicants have canceled claims 1, 18 and 19, solely to expedite prosecution of the remaining claims in the present application, rendering this rejection moot with respect to these claims and claims dependent thereon. Applicants submit that these amendments overcome the Examiner's rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

9. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants submit that the phrase "wherein, as valence and stability permit" is enabled in light of the prior art, because one of skill in the art will recognize that certain functional groups, such as amino and acid chloride, or thioether and peroxyacid, react with each other, thus rendering a compound containing both of such functional groups unstable. Similarly, one of skill in the art will recognize that certain dispositions of functional groups are unstable, such as a geminal diol, which typically dehydrates, e.g., to a ketone or aldehyde. Thus, one of skill in the art would recognize that certain selections of functional groups will result in an unstable or self-reactive compound, and would not need to experiment at all to comprehend the inherent instability of such a compound. Nevertheless, solely to expedite prosecution of the pending

claims, Applicants have removed the term "stability" to obviate the Examiner's rejection. Reconsideration is respectfully requested.

10-11. Claims 3, 5-8, 11, and 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Applicants traverse this rejection to the extent it is maintained over the claims as amended herein.

Claims 3 and 5 are allegedly indefinite for including the terms "e.g.", "preferably", respectively. These terms have been removed from the pending claims to obviate this rejection.

Claims 5-8 are allegedly indefinite for lacking a definition of the various R groups. Applicants have amended these claims to include these definitions, thereby obviating this rejection.

Claim 6 is allegedly indefinite for reciting that "'T and T' taken together with the ring A or B form a covalently closed ring of 5-8 atoms'". This phrase has been amended to obviate this rejection.

12-13. Claims 1, 3, 5-8, and 19-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerashchenko *et al.*

Applicants have canceled claims 1 and 19, solely to expedite prosecution of the remaining claims in the present application, rendering this objection moot with respect to these claims.

Gerashchenko *et al.* teach injecting jervine into the inflamed paws of rats. Claims 3, and 5-8 have been amended and are directed to a method for inhibiting unwanted hair growth comprising administering a composition comprising a purified alkaloid. Therefore, the method taught by Gerashchenko *et al.* does not anticipate claims 3, 5-8, and the claims dependent thereon. Applicants submit that none of the pending claims are anticipated by Gerashchenko *et al.* Withdrawal of this rejection is therefore respectfully requested.

14. Claims 1, 3, 5-8 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Beachy *et al.* ('091).

Applicants have canceled claims 1 and 18, solely to expedite prosecution of the remaining claims in the present application, rendering this objection moot with respect to these claims.

Beachy et al. ('091) teach the compound jervine and its inhibition of cholesterol biosynthesis. Claims 3, and 5-8 have been amended and are directed to a method for inhibiting unwanted hair growth. Therefore, the method taught by Beachy *et al.* does not anticipate claims 3, 5-8, and the claims dependent thereon. Applicants submit that none of the pending claims are anticipated by Beachy *et al* ('091). Withdrawal of this rejection is therefore respectfully requested.

15. Claims 1, 3, 5-8 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Beachy *et al.* ('048).

Applicants have canceled claims 1 and 18, solely to expedite prosecution of the remaining claims in the present application, rendering this objection moot with respect to these claims.

Beachy *et al.* ('048) teach the compounds jervine and cyclopamine and their inhibition of cholesterol biosynthesis. Claims 3 and 5-8 have been amended and are directed to a method for inhibiting unwanted hair growth. Therefore, the method taught by Beachy *et al.* ('048) does not anticipate claims 3, 5-8, and the claims dependent thereon. Applicants submit that none of the pending claims are anticipated by Beachy *et al* ('048). Withdrawal of this rejection is therefore respectfully requested.

16-17. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gerashchenko *et al.* Applicants have canceled claim 18, solely to expedite prosecution of the remaining claims in the present application, rendering this objection moot with respect to this claim. Withdrawal of this rejection is therefore respectfully requested.

18. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beachy *et al.* ('091). Applicants have canceled claim 19, solely to expedite prosecution of the remaining claims in the present application, rendering this objection moot with respect to this claim. Withdrawal of this rejection is therefore respectfully requested.

19. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beachy *et al.* ('048). Applicants have canceled claim 19, solely to expedite prosecution of the remaining claims in the present application, rendering this objection moot with respect to this claim. Withdrawal of this rejection is therefore respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

David P. Halstead, Ph.D.
Reg. No. 44,735

Date: February 28, 2002

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050